SPECIFICATION

Electronic Version 1.2.8

Stylesheet Version 1.0

METHOD AND SYSTEM TO CONDUCT A COMBINATORIAL HIGH THROUGHPUT SCREENING EXPERIMENT

Federal Research Statement

This invention was made with government support under Contract No. 70NAN89H3038 awarded by NIST. The government may have certain rights to the invention.

Background of Invention

[0001] The present invention relates to a method and system to conduct a combinatorial high throughput screening (CHTS) experiment.

[0002] Combinatorial organic synthesis (COS) is a high throughput screening (HTS) method that was developed for pharmaceuticals. COS uses systematic and repetitive synthesis to produce diverse molecular entities formed from sets of chemical "building blocks." As with traditional research, COS relies on experimental synthesis methodology. However instead of synthesizing a single compound, COS exploits automation and miniaturization to produce large libraries of compounds through successive stages, each of which produces a chemical modification of an existing molecule of a preceding stage. Libraries are physical, trackable collections of samples resulting from a definable set of the COS process or reaction steps. The libraries comprise compounds that can be screened for various activities.

[0003] Combinatorial high throughput screening (CHTS) is an HTS method that incorporates characteristics of COS. The CHTS methodology is marked by the

search for high order synergies and effects of complex combinations of experimental variables through the use of large arrays in which multiple factors can be varied through multiple levels. Factors of an experiment can be varied within an array (typically formulation variables) and between an array and a condition (both formulation and processing variables). Results from the CHTS experiment can be used to compare properties of the products in order to discover "leads" formulations and/or processing conditions that indicate commercial potential.

[0004] The steps of a CHTS methodology can be broken down into generic operations including selecting chemicals to be used in an experiment, introducing the chemicals into a formulation system (typically by weighing and dissolving to form stock solutions), combining aliquots of the solutions into formulations or mixtures in a geometrical array (typically by the use of a pipetting robot), processing the array of chemical combinations into products and evaluating the products to produce results.

[0005] Typically, CHTS methodology is characterized by parallel reactions at a micro scale. In one aspect, CHTS can be described as a method comprising (A) an iteration of steps of (i) selecting a set of reactants, (ii) reacting the set and (iii) evaluating a set of products of the reacting step and (B) repeating the iteration of steps (i), (ii) and (iii) wherein a successive set of reactants selected for a step (i) is chosen as a result of an evaluating step (iii) of a preceding iteration.

[0006] The study of catalyzed chemical reactions by CHTS involves the investigation of a complex experimental space characterized by multiple qualitative and quantitative factor levels. Typically, the interactions of a catalyzed chemical reaction such as a carbonylation reaction can involve interactions of an order of 6 or 9 or greater. An investigator must carefully set up a CHTS experiment in order to effectively examine such a complex space. Reactant identities and variables, process identities and variables and levels of combinations of factors, must be chosen to define a space that will provide meaningful results.

[0007] In most instances, an investigator conducts the CHTS experiment for the

benefit of a client, who for example, may be a customer from outside the investigator"s company or co-worker from another department within the company. In any case, the client attempts to clearly articulate its expectations for the experiment to the investigator while at the same time, the investigator articulates capabilities and limitations of the CHTS methodology. It is difficult but critical to translate the articulations of the client and investigator into an experiment definition for the CHTS method. The complexity of a catalyzed chemical experimental space makes translation of needs and capabilities into an experiment definition even more difficult. There is a need for a method and system to conduct an experiment according to specific needs of a client and capabilities of the CHTS method.

Summary of Invention

[0008] The invention meets this need by a providing a method and system to develop an experiment definition for a CHTS experiment. In the method, factors are selected for the experiment and interactions among levels of the factors are estimated. A probability value of positive interactions is then assigned for each of the estimated interactions. A CHTS method is effected on an experimental space representing the levels and the probabilities for each interaction are adjusted according to results of the CHTS method.

[0009] The invention also relates to a system for conducting an experiment. The system comprises a reactor for effecting a CHTS method on an experimental space to produce results and a programmed controller that stores an assigned probability value for estimated positive interactions between levels of factors of the experimental space and adjusts the probabilities for each interaction according to results of the CHTS method.

Brief Description of Drawings

[0010] FIG. 1 is a schematic representation of a system and method for conducting a CHTS experiment.

Detailed Description

[0011] In one embodiment, the invention provides a method and system to permit a client and an investigator to confer to develop an experiment definition for a CHTS experiment. The method and system can utilize a knowledge matrix as a visual and organizational aid to serve as an adjustable definitional model. The matrix model can include the factors of the experimental space to be investigated. Determination of these factors can require selection of reactant identities and levels and selection of process identities and levels and selection of the degrees of combination. For example, the experimental factors of the catalyst of a carbonylation reaction can be two different metals and a solvent. Levels of one metal may be Fe, Cu, Ni, Pb, and Re, of another metal may be V, W, Ce, La and Sn and of the solvent may be dimethylformamide (DMFA), dimethylacetamide (DMAA), tetrahydrofuran (THF), diglyme (DiGly) or diethylacetamide (DEAA). The model can be set up originally to represent an estimation of factor level interactions. The estimation can take the form of a probability. The experiment can be conducted and a value of the matrix can be adjusted between each iteration of the experiment to represent a probability change dictated by the experiment results.

[0012] These and other features will become apparent from the drawings and following detailed discussion, which by way of example without limitation describe preferred embodiments of the present invention.

[0013] FIG. 1 is a schematic representation of a system 10 and method for conducting a CHTS experiment. FIG. 1 shows system 10 including dispensing assembly 12, reactor 14, detector 16 and controller 18. Further shown, is X-Y-Z robotic positioning stage 20, which supports array plate 22 with wells 24. The dispensing assembly 12 includes a battery of pipettes 26 that are controlled by controller 18. X-Y-Z robotic positioning stage 20 is controlled by controller 18 to position wells 24 of the array plate 22 beneath displacement pipettes 26 for delivery of test solutions from reservoirs 28.

[0014] Controller 18 can include a data base repository for storing interaction identifications and probability values input by a client or investigator. The controller 18 also controls aspiration of precursor solution into the battery of

pipettes 26 and sequential positioning of the wells 24 of array plate 22 so that a prescribed stoichiometry and/or composition of reactant and/or catalyst can be delivered to the wells 24. By coordinating activation of the pipettes 26 and movement of plate 22 on the robotic X-Y-Z stage 20, a library of materials can be generated in a two-dimensional array for use in the CHTS method. Also, the controller 18 can be used to control sequence of charging of sample to reactor 14 and to control operation of the reactor 14 and the detector 16. Controller 18 can be a computer, processor, microprocessor or the like.

[0015] An experimental space is defined according to a design that is embodied as a program resident in controller 18. The design uses input from a client and/or an investigator to define interactions and to assign weights that represent probabilities that the interactions will be positive. Controller 18 translates the defined space into a loading specification for array plate 32. Then controller 18 controls the operation of pipettes 26 and stage 20 according to the specification to deliver reactant and/or catalyst to the wells 34 of plate 22.

[0016] Additionally, the controller 18 controls the sequence of charging array plate 22 into the reactor 14, which is synchronized with operation of detector 16. Detector 16 detects products of reaction in the wells 24 of array plate 22 after reaction in reactor 14. Detector 16 can utilize chromotography, infra red spectroscopy, mass spectroscopy, laser mass spectroscopy, microspectroscopy, NMR or the like to determine the constituency of each reaction product. The controller 18 uses data on the sample charged by the pipettes 26 and on the constituency of reaction product for each sample from detector 16 to correlate a detected product with at least one varying parameter of reaction.

[0017]

As an example, if the method and system of FIG.1 is applied to study a carbonylation catalyst and/or to determine optimum carbonylation reaction conditions, the detector 16 analyzes the contents of the well for carbonylated product. In this case, the detector 16 can use Raman spectroscopy. The Raman peak is integrated using the analyzer electronics and the resulting data can be stored in the controller 18. Other analytical methods may be used - for example,

Infrared spectrometry, mass spectrometry, headspace gas-liquid chromatography and fluorescence detection.

[0018] A method of screening complex catalyzed chemical reactions can be conducted in the FIG. 1 system 10. According to the method, a client and an investigator confer to discuss expectations of the experiment to be conducted in the system 10 and the capability of the system to achieve the expectations. The conference can produce a knowledge matrix comprising the experimental space interactions and an assigned weighting to each interaction that represent a first estimate of a probability that the interaction will be a statistically positive interaction, i.e., that the interaction will be a lead. For example, the probabilities can be high, medium and low probabilities. represented respectively by numerical weighting values. "High, medium and low" mean probabilities that are higher, a medium or lower with respect to one another. When three weighting value probabilities are assigned, the values can be in respective ranges of about 0.6 to about 0.99 for high, about 0.2 to about 0.59 for medium and about 0.01 to about 0.19 for low. Desirably, the respective ranges can be about 0.7 to about 0.9, about 0.2 to about 0.5 and about .05 to about 0.15. The knowledge matrix is an adjustable definitional model that represents the estimated interactions and assigned or adjusted probabilities. The model can be a visual organizational aid or the model can be a virtual construct resident in a computer database.

[0019] Formulations and conditions that represent the interactions are then organized according to an experimental design such as a Latin square design or a full factorial design. Formulations are prepared according to the design. For example, a Latin square design can specify a combination of reactants, catalysts and conditions as a multiphase reactant system. In this procedure, a formulation is prepared that represents a first reactant system that is at least partially embodied in a liquid. Each formulation is loaded as a thin film to a respective well 24 of the array plate 22 and the plate 22 is charged into reactor 14. During the subsequent reaction, the liquid of the first reactant system embodied is contacted with a second reactant system at least partially embodied in a gas. The liquid forms a film having a thickness sufficient to allow the reaction rate of the reaction to be

essentially independent of the mass transfer rate of the second reactant system into the liquid.

[0020] In one embodiment, the invention is applied to study a process for preparing diaryl carbonates. Diaryl carbonates such as diphenyl carbonate can be prepared by reaction of hydroxyaromatic compounds such as phenol with oxygen and carbon monoxide in the presence of a catalyst composition comprising a Group VIIIB metal such as palladium or a compound thereof, a bromide source such as a quaternary ammonium or hexaalkylguanidinium bromide and a polyaniline in partially oxidized and partially reduced form. The invention can be applied to screen for a catalyst to prepare a diaryl carbonate by carbonylation.

[0021] Various methods for the preparation of diaryl carbonates by a carbonylation reaction of hydroxyaromatic compounds with carbon monoxide and oxygen have been disclosed. The carbonylation reaction requires a rather complex catalyst. Reference is made, for example, to Chaudhari et al., U.S. Pat. 5,917,077. The catalyst compositions described therein comprise a Group VIIIB metal (i.e., a metal selected from the group consisting of ruthenium, rhodium, palladium, osmium, iridium and platinum) or a complex thereof.

[0022] The catalyst material also includes a bromide source. This may be a quaternary ammonium or quaternary phosphonium bromide or a hexaalkylguanidinium bromide. The guanidinium salts are often preferred; they include the ∀ , T-bis (pentaalkylguanidinium)alkane salts. Salts in which the alkyl groups contain 2-6 carbon atoms and especially tetra-n-butylammonium bromide and hexaethylguanidinium bromide are particularly preferred.

[0023] Other catalytic constituents are necessary in accordance with Chaudhari et al. The constituents include inorganic cocatalysts, typically complexes of cobalt(II) salts with organic compounds capable of forming complexes, especially pentadentate complexes. Illustrative organic compounds of this type are nitrogen-heterocyclic compounds including pyridines, bipyridines, terpyridines, quinolines, isoquinolines and biquinolines; aliphatic polyamines such as ethylenediamine and tetraalkylethylenediamines; crown ethers; aromatic or aliphatic amine ethers such

as cryptanes; and Schiff bases. The especially preferred inorganic cocatalyst in many instances is a cobalt(II) complex with bis-3-(salicylalamino) propylmethylamine.

[0024] Organic cocatalysts may be present. These cocatalysts include various terpyridine, phenanthroline, quinoline and isoquinoline compounds including 2,2':6',2"-terpyridine, 4-methylthio-2,2':6',2"-terpyridine and 2,2':6',2"-terpyridine N-oxide,1,10-phenanthroline, 2,4,7,8-tetramethyl-1,10-phenanthroline, 4,7-diphenyl-1,10, phenanthroline and 3,4,7,8-tetramethy-1,10-phenanthroline. The terpyridines and especially 2,2':6',2"-terpyridine are preferred.

[0025] Another catalyst constituent is a polyaniline in partially oxidized and partially reduced form.

[0026] Any hydroxyaromatic compound may be employed. Monohydroxyaromatic compounds, such as phenol, the cresols, the xylenols and p-cumylphenol are preferred with phenol being most preferred. The method may be employed with dihydroxyaromatic compounds such as resorcinol, hydroquinone and 2,2-bis(4-hydroxyphenyl)propane or "bisphenol A," whereupon the products are polycarbonates.

[0027] Other reagents in the carbonylation process are oxygen and carbon monoxide, which react with the phenol to form the desired diaryl carbonate.

[0028] The following Example is illustrative and should not be construed as a limitation on the scope of the claims unless a limitation is specifically recited.

[0029] EXAMPLEThis example illustrates an identification of an active and selective catalyst for the production of aromatic carbonates. The procedure includes a combination of a experimental team weighting procedure and a CHTS method to identify a best catalyst from a complex chemical space, where the chemical space is defined as an assemblage of possible experimental conditions defined by a set of variable parameters such as formulation ingredient identity or amount or process parameter such as reaction time, temperature, or pressure.

[0030] The chemical space consists of the following TABLE 1 chemical factor levels and TABLE 2 processing factor levels:

TABLE 1

	Formulation Type Parameter Variation	Formulation Amount Parameter Variation
Precious metal catalyst	Held Constant	Held Constant
Primary Transition Metal Cocatalyst (TM)	Fe, Cu, Ni, Pb, Re (as their acetylacetonates)	5,10,20,40 (as molar ratios to precious metal catalyst)
Secondary Metal Cocatalyst (LM)	V, W, Ce, La, Sn (as their acetylacetonates)	5,10,20,40 (as molar ratios to precious metal catalyst)
Cosolvent (CS)	Dimethylformamide (DMFA), Dimethylacetamide (DMAA), Diethyl acetamide (DEAA), Tetrahydrofuran (THF), Diglyme (DiGly)	50,100,200,400 (as molar ratios to precious metal catalyst)
Hydroxyaromatic compound	Held constant	Sufficient added to achieve constant sample volume

[0031] Process parameters are shown in TABLE 2:

TABLE 2

Process Parameter	Parameter Variation
Temperature	Constant at100°C
Pressure	Constant at 1500 psig

[0032] Pre-test estimates of interactions among factor levels are postulated at a meeting between a customer and investigators. The estimates are assigned probability values, which are expressed in the following knowledge matrix TABLE 3. The probabilities are constrained to three possible values, 0.8, 0.3 and 0.1, which express high, medium, and low probabilities. Probabilities of 0.0 and 1.0 are excluded from off-diagonal cells since these probabilities imply complete knowledge. The matrix is symmetrical around the main diagonal, since the probability of A interacting with B is the same as the probability of B interacting with A.

TABLE 3

	TM Type	TM Amount	LM Type	LM Amount	CS Type	CS Amount
TM Type	1	0.8	0.3	0.3	0.3	0.3
TM Amount	0.8	1	0.3	0.1	0.3	0.1
LM Type	0.3	0.3	1	0.8	0.3	0.1
LM Amount	0.3	0.1	0.8	1	0.1	0.1
CS Type	0.3	0.3	0.3	0.1	1	0.8
CS Amount	0.3	0.1	0.1	0.1	0.8	1

[0033]

The matrix information is loaded into a computer database. The computer defines a full factorial experiment according to two factor interactions between levels as shown in TABLE 4. The computer also controls a dispensing assembly and loading robot to load experimental array trays and a reactor to conduct a CHTS experiment. In the experiment, catalyzed mixtures are made up in phenol solvent using the concentrations of each component as given in the rows of TABLE 4. The total volume of each catalyzed mixture is 1.0 ml. From each mixture, a 25 microliter aliquot is dispensed into a 2 ml reaction vial, forming a film on the bottom. The vials are grouped in array plates by process conditions (as specified in the TABLE 2 Pressure and Temperature columns) and each array plate is loaded into a high pressure autoclave and subjected to the reaction conditions specified. At the end of the reaction time, the reactor is cooled and depressurized and the contents of each vial are analyzed for diphenyl carbonate product using a gas chromatographic method. Performance is expressed numerically as a catalyst turnover number or TON. TON is defined as the number of moles of aromatic carbonate produced per mole of Palladium catalyst charged. This is shown in column TON of TABLE 4.

TABLE 4

TMType	LMType	CSType	TMAmt	LMAmt	CSAmt	TON
Ni	V	DiGly	10	5	200	1084
Re	Ce	DEAA	10	10	200	1394
Ni	La	DMFA	10	40	400	1221
Ni	Sn	DEAA	40	5	50	1697
Fe	La	DMAA	10	20	200	949
Pb	Sn	DEAA	40	10	50	2317
Fe	Ce	THF	40	20	100	792
Cu	V	THF	10	10	200	1054
Cu	Sn	DEAA	20	10	100	1058
Cu	La	DMAA	10	40	50	1081
Re	Ce	DMFA	5	40	100	1058
Re	V	THF	5	5	400	1074
Cu	W	DMAA	5	40	400	1125
Cu	Ce	THF	5	10	200	1111
Ni	La	DMFA	20	5	50	1358
Fe	Ce	DMFA	10	20	50	955
Pb	V	DEAA	10	5	100	1040
Cu	V	DMFA	20	40	50	1092
Re	V	DMAA	10	10	100	1080
Re	V	DEAA	10	10	50	1049
Pb	V	DEAA	20	10	400	1043
Pb	Ce	THF	10	10	100	1248
Fe	W	DMAA	40	40	50	914
Ni	La	DMAA	5	20	50	1069
Fe	La	DEAA	5	20	400	1069
Cu	Sn	DiGly	20	40	200	1114
Cu	W	DMFA	40	10	200	1105
Pb	Sn	DMAA	10	40	50	1511
Fe	V	THF	40	10	400	1067
Re	W	DiGly	5	10	400	1034
Cu	W	THF	20	10	400	1041
Pb	La	THF	10	5	50	1371
Pb	V	DMFA	20	10	100	1056
Ni	W	THF	20	5	200	1136
Pb	Sn	DiGly	10	10	200	1499
Re	W	DMFA	40	5	50	1535
Ni	Ce	DEAA	10	20	200	1164
Re	Ce	DEAA	40	20	50	1959
Re	La	DiGly	5	40	200	1077
Pb	La	DEAA	5	40	50	1108
Re	Sn	DiGly	10	40	400	1660
Ni	V	DMFA	5	5	100	1083

Re	La	THF	40	5	200	2396
Re	Sn	DiGly	20	10	100	2291
Fe	Ce	DMFA	5	40	200	1029
Re	W	DMAA	40	5	400	1538
Re	Ce	DiGly	10	20	100	1417
Ni	Ce	DEAA	20	10	400	1251
Re	W	DiGly	20	5	100	1376
Pb	W	THF	5	20	50	1058
Ni	Ce	THF	10	5	100	1236
Cu	V	THF	20	40	100	1078
Fe	Sn	DEAA	10	10	400	837
Fe	La	DMAA	20	20	50	805
Re	V	THF	40	20	50	1076
Pb	W	DiGly	10	20	100	1194
Fe	W	DEAA	10	40	200	1017
Fe	Sn	DiGly	10	5	50	857
Ni	V	DiGly	20	20	100	1065
Ni	Sn	DMAA	40	40	400	1645
Re	Sn	THF	40	10	100	2878
Ni	W	DiGly	40	40	100	1173
Pb	Sn	DEAA	5	5	400	1080
Cu	Ce	THF	40	5	50	1038
Ni	W	DiGly	20	10	200	1215
Ni	Ce	DEAA	20	5	200	1275
Re	V	DiGly	20	5	50	1085
Cu	V	DiGly	10	20	400	1046
Cu	Sn	DMFA	10	5	400	1093
Ni	Ce	DiGly	5	5	50	1069
Pb	V	DiGly	5	40	400	1039
Fe	W	DEAA	40	5	400	936
Fe	W	THF	10	10	100	1043
Re	Ce	DMAA	20	5	100	1705
Ni	W	DMFA	20	20	100	1187
Cu	La	DiGly	5	10	50	1098
Pb	Ce	DMFA	20	40	50	1458
Pb	V	DMAA	5	10	200	1113
Pb	V	DMAA	40	20	50	1072
Ni	Sn	DMAA	5	5	100	1089
Ni	V	THF	20	40	50	1092
Re	La	DMFA	10	20	200	1531
Pb	Ce	DiGly	5	10	50	1067
Cu	Sn	DMAA	5	20	200	1034
Fe	Ce	THF	5	40	400	1105
Pb	V	DMFA	10	40	200	1110
Re	Sn	DMFA	5	10	50	1078
Pb	V	THF	5	20	200	1136

Ni	La	DEAA	10	5	100	1256
Fe	Sn	THF	5	5	200	1056
Pb	La	DMAA	5	40	100	1069
Cu	Ce	DiGly	20	5	400	1110
Ni	W	DEAA	5	40	400	1082
Pb	La	DiGly	5	5	100	1068
Pb	Sn	THF	20	40	400	1851
Cu	La	DMFA	10	10	100	1078
Re	Sn	DiGly	5	20	50	1118
Re	W	THF	10	40	50	1252
Pb	W	DEAA	5	10	200	1040
Cu	V	DEAA	10	5	50	1088
Cu	La	DMFA	40	20	50	1086
Fe	Sn	DMFA	5	40	100	1073
Pb	La	DMFA	40	20	400	1926
Cu	W	THF	5	5	100	1085
Fe	V	DMFA	40	40	400	1106
Ni	Ce	THF	10	10	50	1201
Pb	Ce	DMAA	20	40	200	1460
Fe	Sn	DEAA	20	5	50	711
Ni	Sn	THF	10	40	200	1272
Cu	Ce	DiGly	10	40	50	1059
Pb	Ce	DMAA	40	5	50	1718
Fe	V	DiGly	5	10	100	1060
Pb	W	DMAA	20	10	50	1292
Re	Ce	DMAA	5	40	50	1047
Fe	La	DMAA	20	10	200	792
Re	V	DMFA	5	40	50	1057
Fe	Sn	THF	5	20	400	1045
Ni	V	DiGly	40	10	50	1074
Ni	V	DMAA	20	5	400	1070
Fe	La	DiGly	20	40	100	758
Cu	La	DEAA	5	5	200	1047
Re	La	DiGly	20	20	400	2009
Pb	Ce	DEAA	40	5	100	1695
Re	Sn	DMAA	20	20	400	2255
Pb	La	THF	20	10	200	1701
Pb	W	DMAA	40	20	200	1366
Cu	Sn	THF	5	40	50	1073
Re	Sn	DEAA	5	40	200	1090
Pb	La	DEAA	20	20	100	1677
Pb	W	DiGly	40	5	50	1421
Fe	La	THF	10	40	50	945
Fe	Sn	DiGly	40	40	400	453
Pb	Ce	DEAA	10	40	400	1303
Cu	Sn	DEAA	40	20	400	1102

Ni	La	DEAA	10	5	100	1256
Fe	Sn	THF	5	5	200	1056
Pb	La	DMAA	5	40	100	1069
Cu	Ce	DiGly	20	5	400	1110
Ni	W	DEAA	5	40	400	1082
Pb	La	DiGly	5	5	100	1068
Pb	Sn	THF	20	40	400	1851
Cu	La	DMFA	10	10	100	1078
Re	Sn	DiGly	5	20	50	1118
Re	W	THF	10	40	50	1252
Pb	W	DEAA	5	10	200	1040
Cu	V	DEAA	10	5	50	1088
Cu	La	DMFA	40	20	50	1086
Fe	Sn	DMFA	5	40	100	1073
Pb	La	DMFA	40	20	400	1926
Cu	W	THF	5	5	100	1085
Fe	V	DMFA	40	40	400	1106
Ni	Ce	THF	10	10	50	1201
Pb	Ce	DMAA	20	40	200	1460
Fe	Sn	DEAA	20	5	50	711
Ni	Sn	THF	10	40	200	1272
Cu	Ce	DiGly	10	40	50	1059
Pb	Ce	DMAA	40	5	50	1718
Fe	V	DiGly	5	10	100	1060
Pb	W	DMAA	20	10	50	1292
Re	Ce	DMAA	5	40	50	1047
Fe	La	DMAA	20	10	200	792
Re	V	DMFA	5	40	.50	1057
Fe	Sn	THF	5	20	400	1045
Ni	V	DiGly	40	10	50	1074
Ni	V	DMAA	20	5	400	1070
Fe	La	DiGly	20	40	100	758
Cu	La	DEAA	5	5	200	1047
Re	La	DiGly	20	20	400	2009
Pb	Ce	DEAA	40	5	100	1695
Re	Sn	DMAA	20	20	400	2255
Pb	La	THF	20	10	200	1701
Pb	W	DMAA	40	20	200	1366
Cu	Sn	THF	5	40	50	1073
Re	Sn	DEAA	5	40	200	1090
Pb	La	DEAA	20	20	100	1677
Pb	W	DiGly	40	5	50	1421
Fe	La	THF	10	40	50	945
Fe	Sn	DiGly	40	40	400	453
Pb	Ce	DEAA	10	40	400	1303
Cu	Sn	DEAA	40	20	400	1102

Fe	W	DMFA	20	5	400	963
Cu	Sn	DiGly	5	5	100	1089
Cu	La	THF	40	40	50	1059
Fe	La	DiGly	10	5	400	902
Re	Sn	DMFA	40	40	400	2853
Re	Sn	DiGly	40	40	50	2870
Pb	W	THF	40	40	100	1352
Fe	V	DMAA	5	5	50	1085
Cu	V	DEAA	5	40	100	1060
Re	Sn	DiGly	40	5	400	2917
Pb	Sn	DiGly	40	20	100	2301
Fe	Ce	THF	20	10	50	868
Fe	Ce	DEAA	5	10	100	1071
Re	Ce	DiGly	40	40	400	1987
Re	W	DMFA	20	40	200	1403
Fe	V	DMAA	10	40	100	1102
Cu	W	THF	40	20	200	1059
Re	La	DMFA	20	10	400	1991
Ni	W	DEAA	40	10	100	1225
Ni	W	DiGly	40	20	400	1219
Re	La	THF	20	40	100	1989
Re	La	DEAA	40	10	400	2390
Ni	Sn	DMFA	5	40	200	1096
Re	V	DiGly	40	20	200	1075
Cu	V	DMFA	5	10	400	1112
Ni	Sn	DMAA	20	10	200	1470
Ni	Ce	DMFA	40	40	50	1411
Re	La	DEAA	5	5	50	1102
Fe	W	DMAA	5	5	100	1031
Ni	La	THF	40	5	400	1545
Fe	Sn	DMFA	40	10	200	432
Pb	La	DMAA	10	10	400	1324
Re	Sn	DMAA	10	5	200	1676
Ni	La	DEAA	20	40	200	1341
Fe	Ce	DiGly	10	10	400	995
Re	W	DMAA	5	20	100	1081
Re	Ce	DMFA	10	5	400	1379
Ni	W	DMFA	10	10	400	1075
Cu	W	DEAA	20	40	50	1037
Ni	La	DMAA	40	10	100	1522
Pb	Ce	DMFA	5	20	400	1061
Ni	W	DMAA	10	40	200	1126
Ni	V	DEAA	5	20	400	1107
Re	Ce	DMAA	40	10	200	1919
Ni	Sn	DMFA	20	20	400	1490

[0034]

The results in TABLE 4 are then subjected to an Analysis of Variance (ANOVA) analysis that includes the main effects and all the two-way interactions of the six factors (TM Type, TM Amount, LM type, LM amount, CS Amount, and CS Type). Results of the ANOVA are shown in TABLE 5.

TABLE 5

Source	DF	Seq SS	Adj SS	Adj MS	F	P	
TMType	4	12344279	5926470	1481617	119.24	0.000	
LMType	4	3400185	1381835	345459	27.8	0.000	
TMType*LMType	16	5223338	2724490	170281	13.7	0.000	**
CSType	4	171937	76127	19032	1.53	0.231	
TMType*CSType	16	788408	436537	27284	2.2	0.049	
TMAmount	3	3283677	1543785	514625	41.42	0.000	
TMType*TMAmount	12	6432183	2597860	216488	17.42	0.000	**
LMAmount	3	77667	6773	2258	018	0.908	
TMType*LMAmount	12	331369	195394	16283	1.31	0.287	
CSAmount	3	98658	3220	1073	0.03	0.967	
TMType*CSAmount	12	468170	284193	23683	1.91	0.098	
LMType*CSType	16	216050	364113	22757	1.83	0.100	
LMType*TMAmount	12	1325612	966688	80557	6.48	0.000	**
LMType*LMAmount	12	193246	375448	31287	2.52	0.033	
LMType*CSAmount	12	144330	211215	17601	1.42	0.237	
CSType*TMAmount	12	143455	162020	13502	1.09	0.420	
CSType*LMAmount	12	531604	242598	20217	1.63	0.162	
CSType*CSAmount	12	144681	174047	14504	1.17	0.367	
TMAmount*LMAmount	9	136750	151726	16858	1.36	0.271	
TMAmount*CSAmount	9	140146	109713	12190	0.98	0.484	
LMAmount*CSAmount	9	387333	387333	43037	3.46	0.010	*
Error	20	248520	248520	12426			
Total	224	36231597					

[0035] The client and the investigator observe the rows of TABLE 5 that contain interactions. In the TABLE 5, only three of the interactions, marked **, show very strong evidence of statistical significance (P<0.001), and one, marked *, shows moderately strong evidence (P<0.02). Two show weak evidence (P~0.05). The rest show no evidence of interaction. The client and the investigator then adjust the weighted probabilities in the computer matrix according to the observed statistically significant results. The probabilities are increased for all the strong interactions and decreased for weak interactions. The following algorithm is used as illustrated in TABLE 6: (1) Very strong interaction: increase the matrix amount by half a distance to 1.0. (2) Moderately strong interaction: increase by .25 the

distance to 1.0. (3) Weak evidence: no change. (4) No evidence: decrease by half the distance to zero.

TABLE 6

	TM type	TM Amount	LM type	LM Amount	CS Type	CS Amount
TM type	1	0.8+.1	0.3+.35	0.3-.15	0.3	0.3-.15
TM Amount	0.8+.1	1	0.3+.35	0.1-.05	0.3-.15	0.1-.05
LM type	0.3+.35	0.3+.35	1	0.8	0.3-.15	0.1-.05
LM Amount	0.3-.15	0.1-.05	0.8	1	0.1-.05	0.1+.225
CS Type	0.3	0.3-.15	0.3-.15	0.1-.05	1	0.8-0.4
CS Amount	0.3-.15	0.1-.05	0.1-.05	0.1+.225	0.8-0.4	1

[0036] The revisions shown to TABLE 6, result in TABLE 7.

TABLE 7

	TM type	TM Amount	LM type	LM Amount	CS Type	CS Amount
TM type	1	.9	.65	.15	0.3	.15
TM Amount	.9	1	.65	.05	.15	.05
LM type	.65	.65	1	.8	.15	.05
LM Amount	.15	.05	.8	1	.05	.325
CS Type	0.3	.16	.15	.05	1	.4
CS Amount	.15	.05	.05	.325	.4	1

[0037]

A full factorial experiment is organized and run according to the strongest interactions on the TM Type/TM Amount/LM Type variables (5x4x5 = 100 runs, fully replicated to 200 runs). Results are shown in TABLE 8.

TABLE 8

TMType	LMType	CSType	TM Amount	LM Amount	CS Amount	TON
Fe	V	DMAA	5	10	100	1138
Fe	W	DMAA	5	10	100	1137
Fe	Ce	DMAA	5	10	100	1357
Fe	La	DMAA	5	10	100	1424
Fe	Sn	DMAA	5	10	100	1605
Cu	V	DMAA	5	10	100	1000
Cu	W	DMAA	5	10	100	1040
Cu	Ce	DMAA	5	10	100	1159
Cu	La	DMAA	5	10	100	1176
Cu	Sn	DMAA	5	10	100	1048
Ni	V	DMAA	5	10	100	884
Ni	W	DMAA	5	10	100	896
Ni	Ce	DMAA	5	10	100	905
Ni	La	DMAA	5	10	100	848
Ni	Sn	DMAA	5	10	100	972
Pb	V	DMAA	5	10	100	743
Pb	W	DMAA	5	10	100	965
Pb	Ce	DMAA	5	10	100	585
Pb	La	DMAA	5	10	100	709
Pb	Sn	DMAA	5	10	100	129
Re	V	DMAA	5	10	100	549
Re	W	DMAA	5	10	100	767
Re	Ce	DMAA	5	10	100	491
Re	La	DMAA	5	10	100	726
Re	Sn	DMAA	5	10	100	511
Fe	V	DMAA	10	10	100	1002
Fe	W	DMAA	10	10	100	1038
Fe	Ce	DMAA	10	10	100	1124
Fe	La	DMAA	10	10	100	1211
Fe	Sn	DMAA	10	10	100	1388
Cu	V	DMAA	10	10	100	1000
Cu	W	DMAA	10	10	100	1069
Cu	Ce	DMAA	10	10	100	1064
Cu	La	DMAA	10	10	100	1278
Cu	Sn	DMAA	10	10	100	1269
Ni	V	DMAA	10	10	100	1061
Ni	W	DMAA	10	10	100	1136
Ni	Ce	DMAA	10	10	100	977
Ni	La	DMAA	10	10	100	1001
Ni	Sn	DMAA	10	10	100	1487
Pb	V	DMAA	10	10	100	1048

Pb	W	DMAA	10	10	100	1188
Pb	Ce	DMAA	10	10	100	1333
Pb	La	DMAA	10	10	100	907
Pb	Sn	DMAA	10	10	100	1155
Re	V	DMAA	10	10	100	1028
Re	W	DMAA	10	10	100	839
Re	Ce	DMAA	10	10	100	834
Re	La	DMAA	10	10	100	1308
Re	Sn	DMAA	10	10	100	1203
Fe	V	DMAA	20	10	100	879
Fe	W	DMAA	20	10	100	877
Fe	Ce	DMAA	20	10	100	888
Fe	La	DMAA	20	10	100	983
Fe	Sn	DMAA	20	10	100	759
Cu	V	DMAA	20	10	100	1000
Cu	W	DMAA	20	10	100	1016
Cu	Ce	DMAA	20	10	100	1146
Cu	La	DMAA	20	10	100	1236
Cu	Sn	DMAA	20	10	100	1205
Ni	V	DMAA	20	10	100	1149
Ni	W	DMAA	20	10	100	1062
Ni	Ce	DMAA	20	10	100	1289
Ni	La	DMAA	20	10	100	1374
Ni	Sn	DMAA	20	10	100	1668
Pb	V	DMAA	20	10	100	1126
Pb	W	DMAA	20	10	100	1449
Pb	Ce	DMAA	20	10	100	1476
Pb	La	DMAA	20	10	100	1592
Pb	Sn	DMAA	20	10	100	1828
Re	V	DMAA	20	10	100	1136
Re	W	DMAA	20	10	100	1728
Re	Ce	DMAA	20	10	100	1481
Re	La	DMAA	20	10	100	2336
Re	Sn	DMAA	20	10	100	1928
Fe	V	DMAA	40	10	100	765
Fe	W	DMAA	40	10	100	741
Fe	Ce	DMAA	40	10	100	715
Fe	La	DMAA	40	10	100	475
Fe	Sn	DMAA	40	10	100	590
Cu	V	DMAA	40	10	100	1000
Cu	W	DMAA	40	10	100	1061
Cu	Ce	DMAA	40	10	100	1085
Cu	La	DMAA	40	10	100	1181
Cu	Sn	DMAA	40	10	100	1153
Ni	V	DMAA	40	10	100	1198
Ni	W	DMAA	40	10	100	1367

Ni	Ce	DMAA	40	10	100	1514
Ni	La	DMAA	40	10	100	1754
Ni	Sn	DMAA	40	10	100	1913
Pb	V	DMAA	40	10	100	1477
Pb	W	DMAA	40	10	100	1593
Pb	Ce	DMAA	40	10	100	1980
Pb	La	DMAA	40	10	100	2059
Pb	Sn	DMAA	40	10	100	2252
Re	V	DMAA	40	10	100	1745
Re	W	DMAA	40	10	100	1906
Re	Ce	DMAA	40	10	100	2697
Re	La	DMAA	40	10	100	2606
Re	Sn	DMAA	40	10	100	3245
Fe	V	DMAA	5	10	100	1149
Fe	W	DMAA	5	10	100	1257
Fe	Ce	DMAA	5	10	100	1311
Fe	La	DMAA	5	10	100	1435
Fe	Sn	DMAA	5	10	100	1524
Cu	V	DMAA	5	10	100	1000
Cu	W	DMAA	5	10	100	1032
Cu	Ce	DMAA	5	10	100	1109
Cu	La	DMAA	5	10	100	1077
Cu	Sn	DMAA	5	10	100	1301
Ni	V	DMAA	5	10	100	853
Ni	W	DMAA	5	10	100	910
Ni	Ce	DMAA	5	10	100	863
Ni	La	DMAA	5	10	100	971
Ni	Sn	DMAA	5	10	100	799
Pb	V	DMAA	5	10	100	802
Pb	W	DMAA	5	10	100	828
Pb	Ce	DMAA	5	10	100	913
Pb	La	DMAA	5	10	100	529
Pb	Sn	DMAA	5	10	100	496
Re	V	DMAA	5	10	100	691
Re	W	DMAA	5	10	100	395
Re	Ce	DMAA	5	10	100	372
Re	La	DMAA	5	10	100	455
Re	Sn	DMAA	5	10	100	226
Fe	V	DMAA	10	10	100	912
Fe	W	DMAA	10	10	100	1060
Fe	Ce	DMAA	10	10	100	1104
Fe	La	DMAA	10	10	100	1009
Fe	Sn	DMAA	10	10	100	1091
Cu	V	DMAA	10	10	100	1000
Cu	W	DMAA	10	10	100	1084
Cu	Ce	DMAA	10	10	100	1087

Cu	La	DMAA	10	10	100	1246
Cu	Sn	DMAA	10	10	100	1261
Ni	V	DMAA	10	10	100	983
Ni	W	DMAA	10	10	100	1035
Ni	Ce	DMAA	10	10	100	1238
Ni	La	DMAA	10	10	100	1119
Ni	Sn	DMAA	10	10	100	1188
Pb	V	DMAA	10	10	100	1210
Pb	W	DMAA	10	10	100	965
Pb	Ce	DMAA	10	10	100	1480
Pb	La	DMAA	10	10	100	1038
Pb	Sn	DMAA	10	10	100	1182
Re	V	DMAA	10	10	100	1016
Re	W	DMAA	10	10	100	979
Re	Ce	DMAA	10	10	100	828
Re	La	DMAA	10	10	100	1204
Re	Sn	DMAA	10	10	100	1313
Fe	V	DMAA	20	10	100	874
Fe	W	DMAA	20	10	100	923
Fe	Ce	DMAA	20	10	100	840
Fe	La	DMAA	20	10	100	1017
Fe	Sn	DMAA	20	10	100	700
Cu	V	DMAA	20	10	100	1000
Cu	W	DMAA	20	10	100	1046
Cu	Ce	DMAA	20	10	100	1097
Cu	La	DMAA	20	10	100	1172
Cu	Sn	DMAA	20	10	100	1226
Ni	V	DMAA	20	10	100	1106
Ni	W	DMAA	20	10	100	1249
Ni	Ce	DMAA	20	10	100	1201
Ni	La	DMAA	20	10	100	1331
Ni	Sn	DMAA	20	10	100	1302
Pb	V	DMAA	20	10	100	1362
Pb	W	DMAA	20	10	100	1308
Pb	Ce	DMAA	20	10	100	1665
Pb	La	DMAA	20	10	100	1558
Pb	Sn	DMAA	20	10	100	1942
Re	V	DMAA	20	10	100	1390
Re	W	DMAA	20	10	100	1629
Re	Ce	DMAA	20	10	100	1731
Re	La	DMAA	20	10	100	2401
Re	Sn	DMAA	20	10	100	2327
Fe	V	DMAA	40	10	100	748
Fe	W	DMAA	40	10	100	674
Fe	Ce	DMAA	40	10	100	714
Fe	La	DMAA	40	10	100	691

Fe	Sn	DMAA	40	10	100	610
Cu	V	DMAA	40	10	100	1000
Cu	W	DMAA	40	10	100	1028
Cu	Ce	DMAA	40	10	100	1012
Cu	La	DMAA	40	10	100	1227
Cu	Sn	DMAA	40	10	100	1251
Ni	V	DMAA	40	10	100	1258
Ni	W	DMAA	40	10	100	1351
Ni	Ce	DMAA	40	10	100	1568
Ni	La	DMAA	40	10	100	1576
Ni	Sn	DMAA	40	10	100	1663
Pb	V	DMAA	40	10	100	1437
Pb	W	DMAA	40	10	100	1786
Pb	Ce	DMAA	40	10	100	1933
Pb	La	DMAA	40	10	100	2476
Pb	Sn	DMAA	40	10	100	2126
Re	V	DMAA	40	10	100	1447
Re	W	DMAA	40	10	100	1709
Re	Ce	DMAA	40	10	100	2329
Re	La	DMAA	40	10	100	3067
Re	Sn	DMAA	40	10	100	2904

[0038] An ANOVA analysis of variance of the TABLE 8 data is illustrated in TABLE 9.

TABLE 9

Source	DF	Seq SS	Adj SS	Adj MS	F	P
TMType	4	4777245	4777246	1194311	83.10	0
LMType	4	2432949	2432949	608237	42.32	0
TMAmount	3	10451748	10451748	3483916	242.42	0
TMType*LMType	16	1330652	1330642	83166	5.79	0
TMType*TMAmount	12	22425009	22425009	1868751	130.03	0
LMType*TMAmount	12	1489975	1489975	124186	8.64	0
TMType*LMType*TMAmount	48	3450829	3450829	71892	5.00	0
Error	100	1437139	1437139	14371		
Total	199	47795548				

[0039] The ANOVA analysis detects a statistically significant 3-way interaction, which is a lead to high value formulations with high levels (TMA= 40) of Re in the presence of La or Sn.

[0040] While preferred embodiments of the invention have been described, the present invention is capable of variation and modification and therefore should not be limited to the precise details of the Examples. The invention includes changes and alterations that fall within the purview of the following claims.